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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,356	05/21/2002	Michael Slater	BSW-1	6283

7590 05/09/2006

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,356	SLATER ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-6,8-23 and 34-61* is/are pending in the application.

4a) Of the above claim(s) *34-56* is/are withdrawn from consideration.

5)☐ Claim(s) *12-15* is/are allowed.

6)☐ Claim(s) *1-6,8-11,16-23 and 57-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 8 and 14-18 have been amended. Claims 24-33 have been canceled. claims 57-61 have been aded. Claims 1-6, 8-23 and 34-61 are pending. In order to advance prosecution, claims 11-13 will be examined with the current group, as well as all species of P2X. Claims 34-56 remain withdrawn from consideration. Claims 1-6, 8-23 and 57-61 are under consideration.

2. Sections of Title 35, U.S. Code not found in this action, can be found in a prior action.

3. Claims 16-18 and 59-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear if the "suite" of antibodies encompassed by each claim includes antibodies which are required to bind to the P2X7 receptor subtype, or if the suite requires all antibodies to bind to any P2X receptor subtype. It is noted that page 10 of the specification states that "the "term "suite of antibodies" comprises polyclonal antibodies which contain several different antibodies specific for the same or different antigens and which are able to specifically differentiate between each of the P2X receptor subtypes. When the antibodies are monoclonal, the term "suite of antibodies" also comprises a panel of antibodies able to specifically differentiate between each of the P2X receptor subtypes". The terms relative to a "suite" of antibodies are set forth in open language (comprising) rather than as a definition. It is reasonable to conclude that the recitation on page 10, lines 9-14 is one of preferred embodiments of a "suite of antibodies" encompassed by the instant invention and cannot be construed as a limiting definition because of the open language used in the description..

4. The rejection of claims 1-6, 8-10 and 19-23 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of staging or diagnosing cancer and a method of determining the etiology of carcinogenesis in a mammal, does not reasonably provide enablement for methods of diagnosing a pre-neoplastic state in a mammal is maintained for reasons of record. Claims 11 and 57-60 are also included with this rejection. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

Claims 1-6, 8-11, 19-23 and 57-60 encompass the detection of cancer as well as the detection of a pre-neoplastic state. When given the broadest reasonable interpretation the detection of a pre-neoplastic state encompasses any type of cancer. The art recognizes that the P2X7 receptor is over-expressed in the lymphocytes of patients having Chronic Lymphocytic Leukemia (see 103 rejection below). The art recognizes that leukemia is a clonal disease arising from a single cell (abstract of Jacob et al, Indian J Cancer. 2002 Jun;39(2):61-5 and the abstract of Mauro et al, Curr Opin Oncol. 2001 Jan;13(1):3-7). The art (Meeker et al, Blood. 1989, Vol. 74, pp.1801-1806) teaches that the t(11;14)(q13;q32) translocation is associated with human B-lymphocytic malignancy. Thus it can be construed that a B-cell having acquired said translocation would constitute a leukemic cell. Thus, in order to carry out the claimed methods of detecting a lymphocyte which was going to progress to a leukemic cell it would necessitate that a normal B-cell would over-express the P2X7 receptor before said translocation occurred in said cell. There is no objective evidence with in the specification or any art that this would be the case, therefore one of skill in the art would be subjected to undue experimentation without reasonable expectation of success in order to practice the broadly claimed methods.

Further, the clams encompass the detection of a pre-neoplastic state for solid tumors as well. A pre-neoplastic state in a solid organ or tissue would encompass all stages of progression to a malignant state such as hyperplasia, dysplasia and anaplasia. In order to practice the broadly claimed invention it would be necessary to detect a difference between the P2X7 expression in said cell relative to a corresponding normal cell. The specification has not taught a specific pre-neoplastic stage at which said expression would begin to deviate from the normal, nor has the specification provided evidence that any of the pre-neoplastic stages in any solid tissue or organ would exhibit a deviation in the level of expression of P2X7. Given the lack of teachings in the specification regarding all of the above issues, one of skill in the art would be subject to undue experimentation without reasonable expectation of success.

5. Applicant argues that the specification provides enablement for using P2X detection in differentially staining of benign, hyperplastic and cancerous human prostate tissues on pages 17,

19 and 20 of the specification . It is noted that in the human examples provided data for the P2X1, P2X3 and P2X4 receptors, thus the relevance of the individual subtype of P2X7 as predictive of neoplastic progression in the human prostate is not evident. Applicant has provided exhibit "A" to support the enablement of the invention, but it is noted that the P2X1 and P2X2 rather than the P2X7 receptors were taught by that reference. Applicant has provided exhibit B which teaches that P2X7 expression is indicative of early cancer. However, early cancer is a malignant condition and does not satisfy the requirements of "pre-neoplastic". Further, the instant claims encompass the staging or determination of any neoplastic or pre-neoplastic state in a mammal which is far beyond the single disease of prostate neoplasia, and includes non-solid neoplastic tumors. Applicant has provided exhibits "C" which teaches the intracellular localization of P2X7 in 10% of all breast tissue biopsy samples exhibit atypical hyperplasia, but a strong expression of P2X7 on the cell surface in invasive carcinoma (page 7, first column, lines 1-14 and second column, line 9 to page 8, column 1, line 24). Thus, it is unclear how the initial intracellular expression of P2X7 is indicative of progression because there is no nexus between the tumors having the initial intracellular expression of P2X7 during atypical hyperplasia and the development of subsequent invasive lobular carcinoma or ductal carcinoma in situ. Applicant has provided exhibit D which teaches that labeling for P2X7 was co-localized with superficial spreading of melanoma, but not detected in normal skin samples (page 138, second column, lines 4-8), however the reference does not discuss the labeling of P2X7 in a pre-neoplastic state. It is well accepted in the art that not all tumor antigens are universal, therefore there is no connection between the over expression of an antigen as a certain tissue type progresses through neoplasia and the corresponding expression pattern in a different tissue type as is progresses through neoplasia. It is noted that both cancers of the prostate and breast are dominantly cancers of epithelial tissue which may share common expression patterns, the scope of the claims encompasses non-epithelial cancers such as sarcomas, leukemias, lymphomas and neuroblastomas, and there is no reliable nexus between the alteration of expression patterns and the progression to cancer across these broad classes of malignancy.

6. The rejection of claims 1-3, 8-10, 19-21 under 35 U.S.C. 103(a) as being unpatentable over Altieri et al (WO9216558) in view of Jameison et al (Journal of Cellular Physiology, 1996,

Vol. 166, pp. 637-642) and Buell et al (Blood, 1998, Vol. 92, pp. 3521-3528) is maintained for reasons of record. Claims 58 is also rejected for the same reasons of record.

Claim 1 is drawn in part to a method of staging or diagnosing neoplastic states in a mammal, comprising detecting the P2X7 receptor expression profile of cells and/or tissues from said mammal and comparing the receptor expression profile of normal cells and/or tissues. Claim 2 is drawn to a method of determining the etiology of carcinogenesis in a mammal, comprising detecting the P2X7 receptor expression profile of cells and/or tissues from said mammal and comparing the receptor expression profile of normal cells and/or tissues. Claim 3 embodies the methods of claims 1 or 2 wherein the mammal is a human. Claim 8 embodies the methods of claims 1 or 2 wherein the cells are obtained from a body fluid. Claims 9 and 10 embody the methods of claims 1 or 2 wherein the detection of the P2X7 receptor comprises the use of an antibody reagent, and an antibody reagent specific for P2X7, respectively. Claims 19-22 embody the methods of claims 1 or 2 wherein detection of the P2X7 receptor is by immunohistochemistry, ELISA and RIA, respectively.

Altieri et al teach a method of monitoring treatment of patients afflicted with chronic lymphocytic leukemia in which expression of receptors homologous to factors V and VIII is correlated with the disease state in which the frequency of cells expressing an EPR-1 marker is inversely related to the response to treatment of patients suffering from CLL (page 36, line 3 to page 37, line 19). Altieri et al teach a method of diagnosing CLL and monitoring CLL comprising admixing a body sample containing cells to be assayed for EPR-1 marker with an instant antibody composition which specifically binds to EPR-1 and measuring the amount of immuno-reaction product under predefined reaction conditions wherein the amount of immuno-reaction product formed is correlated to an initial disease state (page 37, lines 21-23). Altieri et al teach that these steps are repeated at a later time during the treatment regimen thereby permitting determination of the patient's response to treatment, with a decrease in the number of EPR-1 molecules expressed on cell surfaces indicating an improvement in the disease state (page 37, lines 23-26). Altieri et al teach monoclonal and polyclonal antibodies to EPR-1 (page 25, lines 19-20 and page 26, lines 27-29), immunohistochemical, ELISA and RIA as methods to detect the EPR-1 protein (page 46, line 26 to page 47, line 23, page 39, line 32 to page 40, line 6,

page 35, lines 20-35). Altieri et al do not teach the P2X7 receptor as a marker for CLL or an antibody which binds specifically to P2X7.

Jameison et al teach that lymphocytes from patients with CLL have higher levels of P2Z receptors than the lymphocytes from normal individuals (Figure 1, and legend). The P2Z receptor is synonymous with the P2X7 receptor. Thus, the teachings of Jameison et al correlate the over-expression of the P2X7 receptor with the presence of CLL.

Buell et al teach a monoclonal antibody which specifically binds to cells which express the receptor and can be used in immunoprecipitations (pp. 3522, second column, last line to page 3224, first column, line 14).

It would have been prima facie obvious at the time the claimed invention was made to substitute the detection of the P2X7 receptor for the detection of the EPR-1 protein in the method taught by Altieri et al. One of skill in the art would have been motivated to do so by the teachings of Jamieson et al on the over-expression of P2X7 on the surface of lymphocytes from patients with CLL. One of skill in the art would understand that the P2X7 protein can serve as a marker for the disease state of CLL in the same sense as EPR-1 in that initial detection of over-expression of P2X7 is diagnostic for CLL and the decrease in the level of P2X7 in response to treatment is indicative of a positive response to treatment and a decrease in malignant lymphocytes, whereas a lack of said decrease in response to treatment would be indicative of non-responsiveness to treatment and an increase in the level of P2X7 would be indicative of the progression of CLL.

7. The rejection of claims 1-3, 8-10, 19-23 and 58 under 35 U.S.C. 103(a) as being unpatentable over Altieri et al (WO9216558) and Jameison et al (Journal of Cellular Physiology, 1996, Vol. 166, pp. 637-642) and Buell et al (Blood, 1998, Vol. 92, pp. 3521-3528) as applied to claims 1-3, 8-10, 19-21 and 58 above, and in further view of Rio et al (WO 9706256) is maintained for reasons of record.

Claim 22 embodies the methods of claims 1 or 2 wherein the detection of the P2X7 receptor is by Western blot, and detection of P2X7 receptor mRNA. The combination of Altieri and Jameison et al and Buell et al does not specifically teach the detection of the P2X7 receptor by Western or mRNA expression.

Rio et al teach the detection of leukemia markers by Western blot and mRNA expression Page 20, lines 7-17 and page 44, lines 12-14)..

It would have been prima facie obvious at the time the claimed invention was made to use the methods of Western blot or mRNA expression for the detection of the P2X7 receptor in the method rendered obvious by the combination of Altieri et al and Jamison et al and Buell et al because the methods of Western blot and mRNA expression measurement are well known in the art and demonstrated to be useful in the detection of leukemia markers.

8. Claims 1-3, 8-10, 19-21, 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altieri et al (WO9216558) in view of Jameison et al (Journal of Cellular Physiology, 1996, Vol. 166, pp. 637-642) and Buell et al (Blood, 1998, Vol. 92, pp. 3521-3528) as applied to claims 1-3, 8-10, 19-21, and 58 above, and further in view of Paul (Fundamental Immunology, Text, 1998, page 170).

Claim 57 specifies that the antibody reagent comprises a polyclonal antiserum. Claim 59 specifies that the antibody reagent of claim 9 is a suite of polyclonal antibodies.

Paul teaches that polyclonal antibodies have advantages over monoclonal antibodies in detection procedures because they bind to multiple distinct sites on an antigen (page 107).

It would have been prima facie obvious at the time the clamed invention was made to use a polyclonal antiserum to PX7 for detection of PX7 in a cellular substrate because polyclonal antisera is taught by the art to bind to more locations on an antigenic site, and thus provide greater binding. When given the broadest reasonable interpretation, the "suite" of polyclonal antibodies required by claim 59 is fulfilled by the polyclonal antiserum which consists of a collection of antibodies, rather than as a discrete antibody.

9. Applicant argues that Alteri does not teach the use of P2X7 as a marker for chronic lymphocytic leukemia, Jamison does not teach that direct detection of P2X7 in lymphocytes of patients having chronic lymphocytic leukemia. Applicant concludes that the combination of references only make it obvious to try the claimed method and that this is not the standard under 35 U.S.C. 103. This has been considered but not found persuasive. The M.P.E.P. (2145) states

"The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.). See the cases cited in O 'Farrell for examples of decisions where the court discussed an improper "obvious to try" approach. See also In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) and In re Ball Corp., 925 F.2d 1480, 18 USPQ2d 1491 (Fed. Cir. 1991) (unpublished) for examples of cases where appellants argued that an improper "obvious to try" standard was applied, but the court found that there was proper motivation to modify the references.

In the instant case the Jamieson reference is relied upon for a detailed methodology regarding the detection of protein antigens which are deferentially expressed on the lymphocytes taken from patients having chronic lymphocytic leukemia. thus the art recognized the technique of leukemia detection by techniques which detect the differential expression of antigens harbored by chronic lymphocytic leukemia cells versus normal cells. Jamison et al teaches that the activity of the P2X7 receptor decreases concomitantly with decreases in the number of chronic lymphocytic leukemia cells. One of skill in the art could reasonable conclude that the decrease in the activity was either due to a modification of the P2X7 receptor as a result of chemotherapy which decreased the activity rather than the level of the receptor, or the decrease in activity was due to a decrease in the receptor level wherein said receptor was being harbored by the malignant

cells. given that the same fact pattern is present in Alteri with respect to a different receptor, EPR-1, and said EPR-1 receptor levels decrease with decreasing levels of malignant cells, one of skill in the art would have a reasonable expectation of success of substituting detection of the P2X7 receptor for the detection of the EPR-1 receptor.

10. Applicant argues that the supporting references do not cure the deficiencies in the initial combination of Alteri, Jamison and Buell. However, because the combination of references is not defective, these arguments are moot.

11. All other objections and rejections are withdrawn in light of applicants amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A Canella, Ph.D.
3/20/2006

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